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Case Report

Recurrent plasma cell myeloma with intracytoplasmic Auer rod-like inclusions after autologous hematopoietic stem cell transplantation

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Abstract: Plasma cell myeloma (PCM) is a bone marrow based neoplastic disorder of plasma cells. The presence of intracytoplasmic Auer rod-like inclusions (ARLIs) in PCM is exceedingly rare. To the best of our knowledge, approximately 40 cases have been published since its first description in 1940. These inclusions are predominantly observed in kappa-restricted, IgG-producing PCM. Only 7 cases of kappa-restricted, IgA-producing PCM with intracytoplasmic ARLIs have been documented in the literature. Here, we reported a rare case of recurrent kappa-restricted, IgA-positive PCM exhibiting intracytoplasmic ARLIs both before and after autologous hematopoietic stem cell transplantation (HSCT). The clinical features, laboratory studies, diagnosis, and management of this case were described. A comprehensive review of the literature was also provided to explore the origin and pathogenesis of these inclusions, and to examine their prognostic implications.

Keywords: Plasma cell myeloma, Auer rod-like inclusions, autologous hematopoietic stem cells transplantation

Introduction

Plasma cell myeloma (PCM) is a bone marrow-based neoplastic disorder of plasma cells, with a clinical course ranging from asymptomatic to aggressive. Various morphologic changes in the neoplastic plasma cells have been reported, including alteration in cytoplasmic volume and color, the presence of cytoplasmic inclusions, and the nuclear-cytoplasmic asynchrony [1].

Intracytoplasmic Auer rod-like inclusions (ARLIs) were first described in plasma cells in 1940 by Steinmann et al., who demonstrated that these inclusions did not represent immunoglobulin deposits [2]. Since then, approximately 40 case reports have documented intracytoplasmic ARLIs in PCM, suggesting a lysosomal origin [2, 3]. Most cases feature kappa-restricted IgG-producing PCM [2], with only 7 reported cases of kappa-restricted, IgA-producing PCM [2, 4-7].

Autologous hematopoietic stem cell transplantation (HSCT) remains the standard of care for young patients (usually limited to 65 years old) with newly diagnosed PCM [8]. However, inevitable relapses remain, threatening long-term remission [8]. Here, we present the first documented case of recurrent kappa-restricted IgA PCM exhibiting the same intracytoplasmic ARLIs both before and after autologous HSCT.

Case presentation

A 69-year-old male patient had recurrent PCM. His initial hematology evaluation in early 2016 showed a serum IgA level of 2400 mg/dL, IgG of 700 mg/dL, and IgM of 38 mg/dL. Serum protein electrophoresis (SPEP) revealed an M-spike of 1.68 g/dL, and serum immunofixation conformed an IgA kappa monoclonal protein. Bone marrow biopsy showed marked hypercellularity (90%), with CD138-positive plasma cells comprising approximately 30-40% of the marrow cellular element (**Figure 1A**, **1B**).

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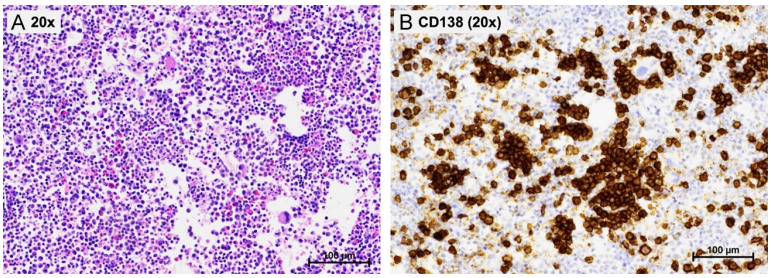

Figure 1. Bone marrow biopsy from 2016. A. H&E-stained section shows sheets and clusters of plasma cells (20×). B. CD138 immunohistochemical staining highlights these plasma cells.

Most neoplastic plasma cells exhibited anaplastic features, including prominent nucleoli and occasionally bilobated nuclei (**Figure 2A**, **2B**). Some cells contained multiple intracytoplasmic ARLIs resembling classic Auer rods (**Figure 2C**). Flow cytometry identified 2% kappa-restricted plasma cells expressing CD38, CD138, and CD56. Magnetic resonance imaging (MRI) of the pelvis showed diffusely abnormal marrow signal involving the pelvic and proximal femora, suggestive of an infiltrative process, but no discrete lytic lesions. These findings led to a diagnosis of IgA kappa-restricted smoldering PCM.

In the spring of 2017, a second bone marrow biopsy showed 30% clonal plasma cells and cytogenetic analysis revealed trisomy of chromosomes 6, 7, 9, and 15 along with monosomy 13. A 24-hour urine collection contained 1566 mg of protein, with an M-spike of 1227 mg. By the end of 2017, a positron emission tomography (PET) scan demonstrated diffuse bone marrow involvement without specific focal lytic lesions. Although the patient exhibited no acute kidney injury or worsening anemia through early 2018, his monoclonal paraprotein levels continued to rise. Consequently, he began therapy with lenalidomide and dexamethasone, followed by an autologous HSCT in the summer of 2018. A subsequent bone marrow biopsy in the fall of 2018 showed no residual PCM, and the patient thereafter continued on maintenance lenalidomide.

The patient remained in remission through early 2023, when his kappa free light chain levels began to rise (188.07 mg/L), while lambda free light chain levels remained normal (21.12 mg/L). Serum immunofixation demonstrated a faint band of IgA kappa monoclonal protein. Four months later, a bone marrow biopsy revealed 10-20% Kappa-restricted, IgA-positive plasma cells, consistent with recurrent PCM (**Figure 3A-F**). Most neoplastic plasma cells appeared relatively normal in morphology, yet a higher proportion contained multiple intracytoplasmic ARLIs compared to the more anaplastic features noted in the initial 2016 diagnostic biopsy (**Figure 4A**, **4B**). Flow cytometry confirmed a similar immunophenotype. Following this confirmed relapse, the patient underwent radiation therapy and received Zometa infusion.

Genetic testing of the recurrent PCM bone marrow specimen showed a normal male karyotype. Fluorescence *in situ* hybridization (FISH) analysis of CD138 positive enriched plasma cells identified trisomy 5 in 12% of cells (12/100), a gain of one copy of 6p21.1 (CCND3 locus) in 9% of cells (9/100) without CCND3::IGH fusions, monosomy 13 (loss one copy of D13S319 and LAMP loci) in 14% of cells (14/100), and a partial 5'IGH gene deletion without IGH gene rearrangement at 14q32 in 12% of cells (12/100) (**Figure 5A-D**). No additional abnormalities were detected in 100 nuclei/probe examined. Moreover, a Pan-heme next generation sequencing (NGS) panel did not reveal any pathogenic or likely pathogenic variants, nor variants of undetermined significance.

Discussion

Morphologic variations of neoplastic plasma cells in PCM can generally be grouped into three categories [1]: (1) plasma cells with reduced cytoplasm (lymphoplasmacytoid myeloma), (2) nuclear-cytoplasmic asynchrony (immature myeloma), and (3) cytoplasmic anomalies, including changes in color (flame cells), round inclusions (Mott cells, Russell bodies), Auer rod-like inclusions (ARLIs), and crystalline inclusions. Although true Auer rods are most often observed in acute promyelocytic leukemia (APL) [9], ARLIs have been reported in non-myeloid hematologic neoplasms, such as plasma cell neoplasms [2], less frequently, in non-Hodgkin lymphomas [10], early T-cell precursor

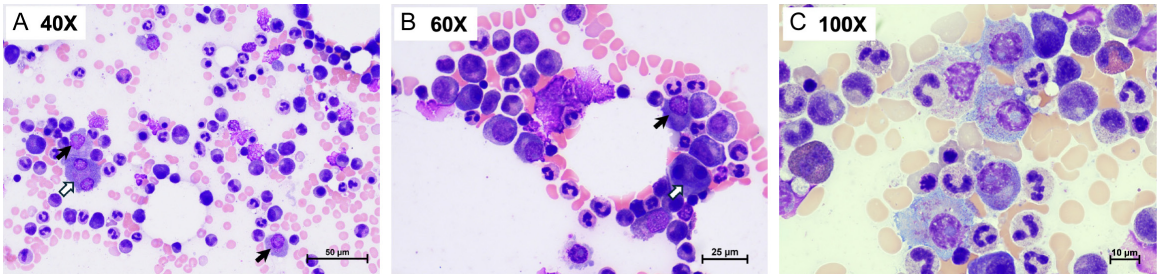

Figure 2. Bone marrow aspirate smears from 2016. A, B. Anaplastic plasma cells with prominent nucleoli (black arrow) and bilobated nuclei (white arrow) shown at 40× and 60× magnification, respectively. C. Anaplastic plasma cells containing bundles of intracytoplasmic Auer rod-like inclusions (ARLIs) (100×).

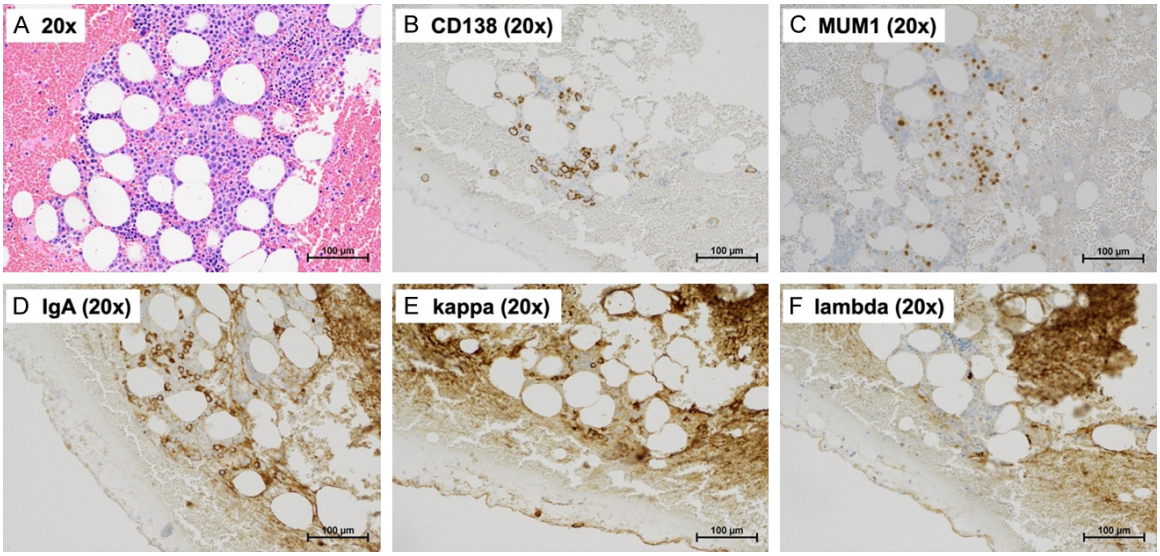

Figure 3. Bone marrow clot section from the 2023 recurrence. A. H&E-stained section (20×) showing clusters of plasma cells. B, C. Immunohistochemical staining with CD138 and MUM1 highlighting the plasma cells. D-F. Demonstration of kappa-restricted, IgA-positive plasma cells.

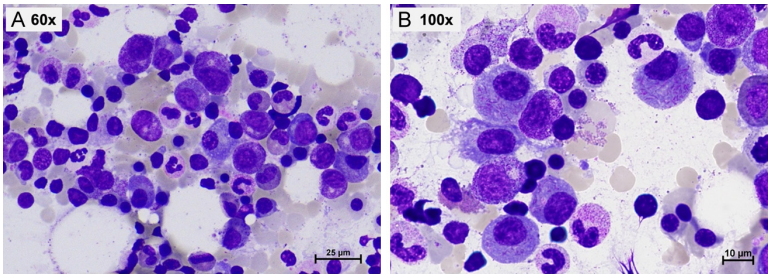

Figure 4. Bone marrow aspirate smears from the 2023 recurrence, showing mature plasma cells with bundles of intracytoplasmic Auer rod-like inclusions (ARLIs) (A. 60×, B. 100×).

acute leukemia (ETP-ALL) [11], the now-defunct B-cell prolymphocytic leukemia (PLL) [12], and even non-hematologic malignancies, including medullary carcinoma of thyroid [13].

Metzgeroth et al. demonstrated α-N-esterase expression within the intracytoplasmic ARLIs in PCM, suggesting a lysosomal origin [3]. By transmission electron microscopy (EM), they proposed that intracytoplasmic ARLIs formed through the fusion of primary granules and had a close relationship to myeloid Auer rods [3]. Based on cases published up to 2009, Hutter et al. summarized that ARLIs might be positive for α-Naphthyl acetate esterase (ANAE), acid phosphatase, β-Glucuronidase, hematoxylin-phloxine saffron, and weakly positive with hematoxylin-eosin, while negative

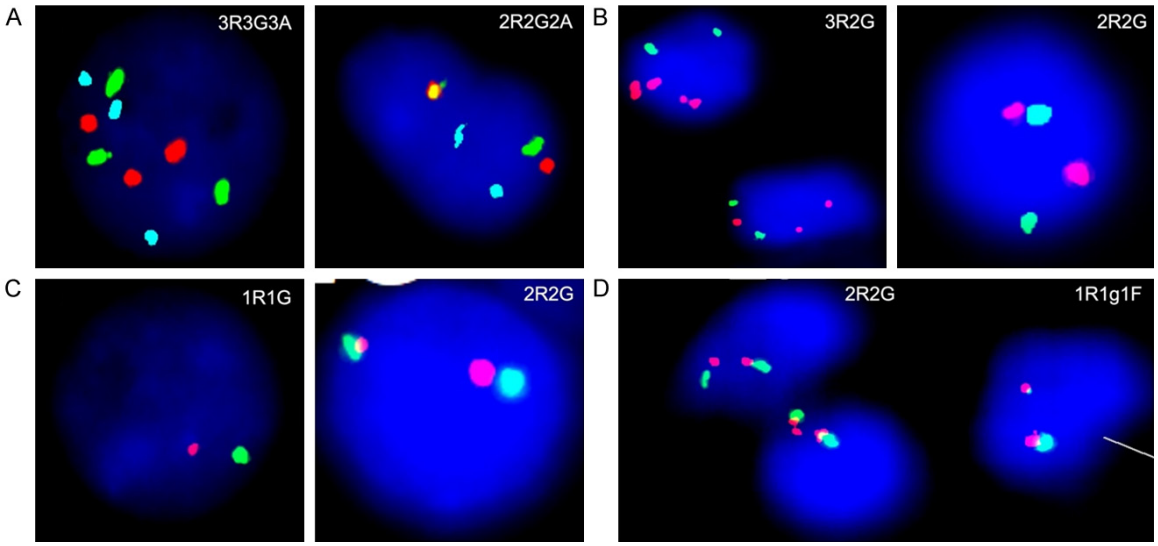

Figure 5. FISH studies of CD138-positive enriched plasma cells showing different abnormalities. A. Trisomy 5 (Red: EGR1/5q31, Green: RPS14/5q33, Aqua: D5S1518/5p15). B. Gain of one copy of 6p21.1 (CCND3 locus) (Red: CCND3/6p21, Green: IGH/14q32). C. Monosomy 13 (loss one copy of D13S319 and LAMP loci) (Red: D13S319/13q14.2, Green: LAMP 13q34). D. Partial 5'IGH gene deletion at 14q32 (Red: 3'IGH, Green: 5'IGH).

Table 1. Summary of the clinicopathologic features from all reported cases and our case of plasma cell myeloma (PCM) exhibiting intracytoplasmic Auer rod-like inclusions (ARLIs)

Paraprotein	All cases	Male	Female
IgG-κ	19	14	5
IgG-λ	1	1	0
IgA-κ	8	5	3
IgM-κ	1	1	0
IgG/M-κ	1	1	0
κ-LC	6	2	4
Bence-Jones	3	1	2
Not reported	3	1	2
Total	42	26	16
Age of onset (range)	34-79	34-79	38-73
Age of onset (mean)	58.1	58.4	57.7

for amyloid A, peroxidase, Sudan black B, chloroacetate esterase, PAS, butyrate esterase, Congo red, thioflavin T, Luxol fast blue, methyl green, oil red O, and alkaline phosphate [2]. However, one case of ARLIs staining positive for peroxidase (POX) has been reported [14]. In addition, a PCM case featuring atypical plasma cells co-expressing myeloid markers (CD13, CD33) and containing bundles of ARLIs has also been described [15].

Among all the published cases [2, 4-7, 14-28] and our case, there are 16 female patients whose age at onset ranged from 38 to 73 years (mean 57.7 years), and 26 male patients ranging from 34 to 79 years (mean 58.4 years). The average age at onset for PCM with intracytoplasmic ARLIs appears to be similar for both sexes, but possibly lower than the overall average age of 70 years commonly reported for PCM diagnoses (**Table 1**) [29].

In our case, the neoplastic plasma cells exhibited anaplastic features in the initial diagnosis but appeared relatively mature at recurrence following autologous HSCT. The intracytoplasmic ARLIs were present in both cases and seemed to increase in number upon recurrence. Several prognostic factors in this patient's 2016 smoldering PCM suggested a high risk of recurrence and rapid progression - particularly the IgA subtype of M protein and diffused bone marrow abnormalities on MRI [30]. Notably, Kyle *et al.* observed a significantly shorter time to progression in patients with IgA smoldering PCM compared to those with IgG [31]. Regarding the FISH findings in CD138 positive enriched plasma cells, trisomy 5 is consistent with an underlying hyperdiploid karyotype, which is generally linked to standard risk PCM. Deletion of 13q is associated with an intermediate risk, whereas the prog-

nostic significance of 5'IGH gene deletion remains unclear.

Crystalline inclusions in plasma cells have been reported in association with adult Fanconi syndrome (FS) [1] and crystal-storing histiocytosis [32], both of which often occur in monoclonal gammopathies involving kappa light chains. However, in our patient, renal function remained normal at both initial diagnosis and during recurrence. Clinicians should nevertheless be vigilant for monoclonal gammopathy of renal significance if crystalline inclusions are identified in plasma cells, and renal function should be evaluated accordingly [1].

Autologous HSCT is the standard of care for newly diagnosed PCM in younger patients and, in select cases, fit older adults [8]. However, the procedure remains limited by the risk of relapses, posing a challenge for sustained remission. In 2016, our patient was 62 years old with no severe comorbidities and thus a suitable candidate for autologous HSCT, which he received in 2018. Despite this intervention, his PCM recured in early 2023.

Conclusion

To the best of our knowledge, this is the first reported case of recurrent kappa-restricted IgA PCM exhibiting intracytoplasmic ARLIs both before and after autologous HSCT. Initially, the neoplastic plasma cells displayed anaplastic features, whereas they appeared more mature upon recurrence. Although previous reports have noted an association between adult Fanconi syndrome and ARLIs in PCM, our patient did not show any evidence of renal dysfunction. Nevertheless, the presence of crystalline inclusions in plasma cells of patients with monoclonal gammopathy may indicate potential renal involvement. The prognostic significance of intracytoplasmic ARLIs in PCM remains uncertain. Given the rarity of these findings, multi-institutional collaboration is warranted to identify additional cases and perform retrospective cohort analyses that may clarify the correlations between ARLIs, clinicopathologic features, and patient outcome in PCM.

Disclosure of conflict of interest

None.

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References

[1] Ribourtout B and Zandecki M. Plasma cell morphology in multiple myeloma and related disorders. Morphologie 2015; 99: 38-62.
[2] Hutter G, Nowak D, Blau IW and Thiel E. Auer rod-like intracytoplasmic inclusions in multiple myeloma. A case report and review of the literature. Int J Lab Hematol 2009; 31: 236-240.
[3] Metzgeroth G, Back W, Maywald O, Schatz M, Willer A, Hehlmann R and Hastka J. Auer rod-like inclusions in multiple myeloma. Ann Hematol 2003; 82: 57-60.
[4] Daneshbod Y, Kumar PV and Tabei SZ. IgA myeloma with quadrangular crystalline inclusions. Haematologica 2004; 89: EIM18.
[5] Sharma P, Sachdeva MUS, Ahluwalia J and Malhotra P. Plasma cells with hairy projections and Auer rod-like inclusions in a patient with multiple myeloma. BMJ Case Rep 2017; 2017: bcr2017221315.
[6] Khan SP, Khan MA, Khan FP, Bhat S, Geelani S and Rasool J. Auer rod-like inclusions in multiple myeloma: first case report from the Kashmir Valley. International Journal of Research and Review 2019; 6: 178-180.
[7] Mathur A, Bansal S, Sharma U and Talwar A. Auer rod-like inclusions in multiple myeloma: report of two diagnostically challenging cases. Indian J Cancer 2022; 59: 110-114.
[8] Pasvolsky O, Wang Z, Milton DR, Tanner MR, Bashir Q, Srour S, Saini N, Lin P, Ramdial J, Nieto Y, Tang G, Kebriaei P, Aljawai Y, Khan HN, Lee HC, Ye C, Patel KK, Thomas SK, Orlowski RZ, Shpall EJ, Champlin RE and Qazilbash MH. Multiple myeloma patients with a long remission after autologous hematopoietic stem cell transplantation. Blood Cancer J 2024; 14: 82.
[9] Sehgal T and Sharma P. Auer rods and faggot cells: a review of the history, significance and mimics of two morphological curiosities of enduring relevance. Eur J Haematol 2023; 110: 14-23.
[10] Gao Z, Cui F, Liu M, Guo Y, Hu Y and Shi M. Auer rod-like inclusions in the cytoplasm of B-cell lymphoma cells with bone marrow infiltration. Exp Hematol 2019; 77: 6-11.
[11] Rahman K, Singh P, Chandra D, Dev Yadav D, Gupta R and Gupta A. Early T-cell precursor acute lymphoblastic leukemia with Auer rods-a

case report. Int J Lab Hematol 2020; 42: e27-e29.
[12] Zhao Y and Lv J. Auer rod-like inclusions in B-cell prolymphocytic leukemia. Turk J Haematol 2019; 36: 280-281.
[13] Mohammadnia Avval M, Kumar PV and Dehghani F. Multiple auer rods in fine-needle aspiration smears of medullary thyroid carcinoma: an unusual finding. Int Med Case Rep J 2020; 13: 85-88.
[14] Zhu L, An L, Zhang XY, Ren XR and Song JW. Peroxidase-positive Auer bodies in plasma cells in multiple myeloma: a case report. Int J Clin Exp Pathol 2015; 8: 15301-15306.
[15] Keutgens A, Foguenne J, Gothot A and Tassin F. Atypical plasma cells with coexpression of myeloid markers and bundles of Auer rod-like inclusions. Int J Lab Hematol 2015; 37: e85-86.
[16] Ali N and Moiz B. Azurophilic inclusions in plasma cells. Singapore Med J 2009; 50: e114-115.
[17] Oh SH and Park CJ. Auer rod-like crystal inclusions in plasma cells of multiple myeloma. Korean J Hematol 2010; 45: 222.
[18] Kulbacki EL and Wang E. IgG-lambda plasma cell myeloma with cytoplasmic azurophilic inclusion bodies. Am J Hematol 2010; 85: 516-517.
[19] Noujaim JC and D'Angelo G. Auer rod-like inclusions in kappa light chain myeloma. Blood 2013; 122: 2932.
[20] Abdulsalam AH and Bain BJ. Auer-rod like inclusions in multiple myeloma. Am J Hematol 2014; 89: 338.
[21] Ho WK and Zantomio D. Auer rod-like inclusions in plasma cells in multiple myeloma. J Clin Pathol 2014; 67: 547-548.
[22] Zhang J, Li Y, Li S, Jiang X, Meng Y, Li M, He Y and Huang W. Auer rod-like inclusions and hemophagocytosis in neoplastic cells of multiple myeloma. Hematol Transfus Int J 2015; 1: 65-66.
[23] Tejwani N, Tyagi S and Dass J. Multiple auer rod like inclusions in multiple myeloma. Indian J Hematol Blood Transfus 2017; 33: 121-122.
[24] Sylvia MT, Jacob SE and Basu D. Multiple myeloma with crystalline and Auer rod-like inclusions. Br J Haematol 2017; 179: 8.
[25] Enko D and Kriegshauser G. Light chain myeloma with highly atypical plasma cells and extensive auer rod-like inclusions. Turk J Haematol 2019; 36: 61-62.
[26] Hayashino K, Matsuda M, Negoro T, Fujishita K and Imai T. A rare case of multiple myeloma with Auer rod-like inclusions in plasma cells. Int J Hematol 2022; 116: 461-462.
[27] Bouanani N, Achour L, Yahyaoui A and Youssefi H. Auer rod-like inclusions in a patient with multiple myeloma. Balkan Med J 2022; 39: 446-447.
[28] Luo Q, Ma Q and Zhang S. A case of multiple myeloma with auer rod-like inclusions in plasma cells. Clin Lab 2025; 71.
[29] Urban VS, Cegledi A and Mikala G. Multiple myeloma, a quintessential malignant disease of aging: a geroscience perspective on pathogenesis and treatment. Geroscience 2023; 45: 727-746.
[30] Rajkumar SV, Kumar S, Lonial S and Mateos MV. Smoldering multiple myeloma current treatment algorithms. Blood Cancer J 2022; 12: 129.
[31] Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, Larson DR, Plevak MF, Jelinek DF, Fonseca R, Melton LJ 3rd and Rajkumar SV. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med 2007; 356: 2582-2590.
[32] Zhu L, Wang L, Shi H, Jiang L, Li X, Shao C, Yan Y, Dong B, Zou W and Zuo L. Combined crystal-storing histiocytosis, light chain proximal tubulopathy, and light chain crystalline podocytopathy in a patient with multiple myeloma: a case report and literature review. Ren Fail 2023; 45: 2145970.